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Review

Are biological sensors modulated by their structural scaffolds? The role of the structural muscle proteins α-actinin-2 and α-actinin-3 as modulators of biological sensors

Monkol Lek, Kathryn N. North *

Institute for Neuroscience and Muscle Research, The Children's Hospital at Westmead, Sydney 2145, NSW, Australia
Discipline of Paediatrics and Child Health, Faculty of Medicine, University of Sydney, Sydney 2006, NSW, Australia

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ABSTRACT

Biological sensors and their ability to detect and respond to change in the cellular environment can be modulated by protein scaffolds acting within their interaction network. The skeletal muscle α-actinins have been considered as primarily structural scaffold proteins. However, deficiency of α-actinin-3 due to a common null polymorphism results in predominantly metabolic changes in skeletal muscle function. In this review, we explore the range of phenotypes associated with α-actinin-3 deficiency, and draw supporting evidence from known interaction partners for its role as a scaffold which acts to modulate biological sensors that result in changes in muscle metabolism and structure.

1. Introduction

The α-actinins are a family of four actin-binding proteins (two muscle and two non-muscle isoforms) that have high sequence similarity and share a number of functional domains: an N-terminal actin-binding domain, a central rod domain consisting of spectrin like repeats, and a C-terminal region that contains EF-hand motifs (Fig. 1A) [1]. The skeletal muscle α-actinins (encoded by the *ACTN2* and *ACTN3* genes) were initially characterized as structural components of the contractile apparatus of muscle fibres [2]. *ACTN2* is expressed in all muscle fibres, whereas *ACTN3* has evolved to have a highly specialised pattern of expression in only fast glycolytic muscle fibres [3]. There is a common null polymorphism (R577X) in *ACTN3* that results in absence of α-actinin-3 in more than one billion humans worldwide [4]. Although the R577X polymorphism does not result in any overt disease phenotype, its association with muscle performance has been widely studied in athletes from around the world [5]. The R allele is advantageous and the X allele is detrimental in sports which require muscle strength and power; the X allele demonstrates some benefit in sports that require muscle endurance, although the association is less strong [6]. In addition, *ACTN3* genotype contributes to variation in muscle strength within the general population [7,8]. Intriguingly, *ACTN3* is one of only two genes in humans in which positive selection for a null mutation [9] (i.e. X allele) along with a higher frequency in non-African populations, has been identified to date – suggesting a selective advantage within the Eurasian environment [4].

In order to study the effects of α-actinin-3 deficiency on muscle function, the *Actn3* knockout (KO) mouse was generated. The closely related protein, α-actinin-2, is up-regulated and expressed in all fibre types in KO mice, similar to the expression pattern seen in human muscle. The increased expression of α-actinin-2 in fast glycolytic muscle fibres is sufficient to avoid muscle disease but does not completely compensate for the absence of α-actinin-3. At the physiological level, *Actn3* KO mice have decreased muscle strength, enhanced muscle endurance and a significant reduction in muscle mass compared to wild-type (WT) due to decreased diameter of fast twitch (2B) muscle fibres in which α-actinin-3 is expressed [4,10]. In addition, isolated *Actn3* KO muscles have longer twitch half-relaxation times and enhanced recovery from fatigue compared to WT [11]. At the molecular level, KO muscle fibres showed an overall increase in glycogen content, while fast fibres display significantly decreased activity of enzymes in the anaerobic pathway and increased activity of mitochondrial enzymes in the oxidative pathway [4,10]. Taken together, these observations

* Corresponding author at: Institute for Neuroscience and Muscle Research, The Children's Hospital at Westmead, Sydney 2145, NSW, Australia.
E-mail address: kathryn@chw.edu.au (K.N. North).

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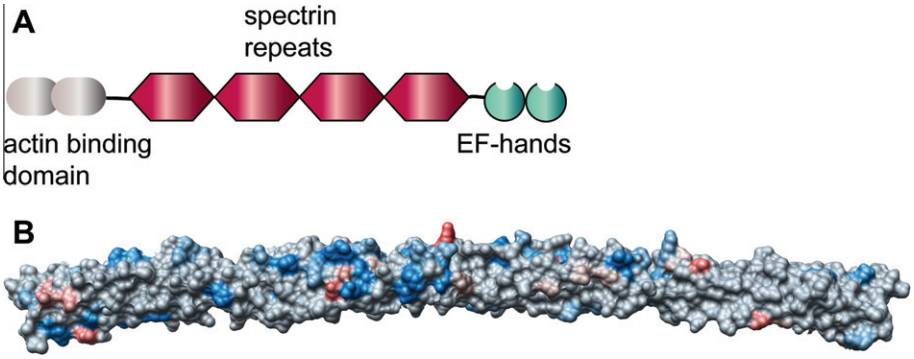

Fig. 1. (A) The highly conserved domain structure of α-actinin which contains an actin-binding domain, four spectrin repeats and EF-hand domains. (B) Surface representation of α-actinin rod domain (1HCI), aligned with spectrin repeat 1 on the left and spectrin repeat 4 on the right. The colors grey, blue and red represent identical, conservative and non-conservative residue substitutions when α-actinin-2 and -3 vertebrate sequences are aligned.

suggests a shift towards a slow oxidative muscle phenotype and thus provide an explanation for poorer sprint and improved endurance performance in *ACTN3* XX humans.

Despite comprehensive characterization of the *Actn3* KO mouse model, the underlying molecular mechanisms that link the absence of a structural protein to the reported phenotype remains elusive. Staining for myosin heavy chain isoforms (MyHC) demonstrate no changes in fibre type proportions in KO muscle. In contrast, transgenic mice modelling the effects of alterations in PGC-1α, PPAR, calsarcin-2 and calcineurin on muscle metabolism all show an activation of slow oxidative gene programs resulting in a shift to a slow oxidative phenotype and increased numbers of slow fibres as defined by MyHC. Similarly, the ablation of metabolic enzymes, glycogen synthase [12], hormone sensitive lipase [13] and phosphofructo-1-kinase [14] also induce shifts in fibre types through the activation of gene programs which couple metabolic and structural muscle gene expression. In contrast, the ablation of structural proteins, desmin [15], myotilin [16], αβ-crystallin [17], myosin heavy chain IIb and IIx [18], can produce structural abnormalities but do not cause a shift in metabolic properties or fibre types. Thus, the structural protein α-actinin-3 is unique in its ability to induce a shift in both metabolic and structural properties of muscle fibres without influencing muscle fibre type as defined by the expression of myosin heavy chain isoform.

In this review, we define a biological sensor as a protein or protein complex with the ability to detect signals in the form of energy (e.g. electrical, mechanical) or molecules (calcium) and respond by activating or modulating biological processes. The biological sensors, calmodulin (calcium sensor) [19], voltage gated potassium channel (electrical) [20] and the cardiac stretch sensor (mechanical) [21] are examples of well-characterized sensors. The ability to detect and respond to changing extra-cellular and intra-cellular environments is critical for cell survival. Hence, the ability of a biological sensor to detect changing environments serves as an important precursor to cellular response.

The sarcomeric α-actinins (α-actinin-2 and -3) are notable amongst the structural proteins in their ability to interact with a diverse range of structural, membrane, signalling and metabolic proteins [1]. For a comprehensive review of α-actinins and their interaction partners, refer to the follow reviews [1,22,23]. In addition to proteins, α-actinin binds to calcium [24] and PIP2 [25] which regulates its affinity for actin. The functional EF-hand domains within the non-muscle actinins allow them to behave as a calcium sensor responsible for cytoskeletal remodelling [26]. This function is conserved in all invertebrate actinins and non-muscle actinins but appears to be lost due to deletion in the EF-hand in some vertebrate skeletal muscle (sarcomeric) α-actinins including in humans and mice [27]. The α-actinin rod domain is composed of four spectrin like repeats and mediates the majority of these interactions. Furthermore, at a protein complex level, α-actinins form components of sensor machinery through direct protein interactions both at the membrane (voltage, ligand and mechanical stretch sensors) and the Z-line (mechanical stretch, calcium and metabolic sensors). Although the sarcomeric α-actinins do not function as sensors themselves, they act as scaffolds and have been shown to play a role in regulation in terms of number, location and activation threshold of sensors. Interestingly, mutations within α-actinin-2 and its interaction partners of the sensor machinery result in cardiomyopathy due to altered binding affinity [28–30]. The protein sequence of α-actinin-2 and α-actinin-3 are 80% identical [3] and thus sites which differ are effectively missense mutations. The conservation of non-conservative residue changes since the duplication and divergence of α-actinin-2 and α-actinin-3 (Fig. 1B) may contribute to subtle differences in protein interaction such as selectivity amongst interaction partners for a specific sarcomeric isoform. In the absence of α-actinin-3 we propose three general possibilities that may alter the function of sensor machinery: (1) The absence of α-actinin-3 specific interactions and the presence of α-actinin-2 specific interaction within fast glycolytic fibres. (2) Altered protein complex stability due to changes in affinity for α-actinin-2. (3) Fast muscle fibres deficient in α-actinin-3 may be more susceptible to damage and release proteins capable of transport to the nucleus (Fig. 2). This provides an alternate protein interaction framework to explain how muscle fibre properties can be changed, and these changes may lie upstream to those induced by PGC1-α, PPAR and calcineurin pathways. On this basis we have reviewed the known protein interactions of the sarcomeric α-actinins, with a focus on defining the biological sensors that may be modulated by the α-actinins to induce changes in muscle metabolism and structure without altering fibre type specification.

2. Membrane sensors

The localization of channels and receptors on the cell membrane allows them to act as biological sensors that detect extra-cellular signals such as molecules, mechanical and electrical signalling. The α-actinins interact with a diverse range of channels and receptors which make up the sensor machinery, and thus have a much more diverse role than the "structural" role that they were originally thought to play in maintaining Z-line structure and an ordered myofibrillar array [2]. The sarcomeric α-actinins have now been shown to interact with, and modify, the properties of the following sensors at the membrane: (1) Interactions with α-actinin regulate the membrane density for the adenosine A_{2A} [31] and acetylcholine receptors [32] and the ion channels $K_v1.5$ [33]

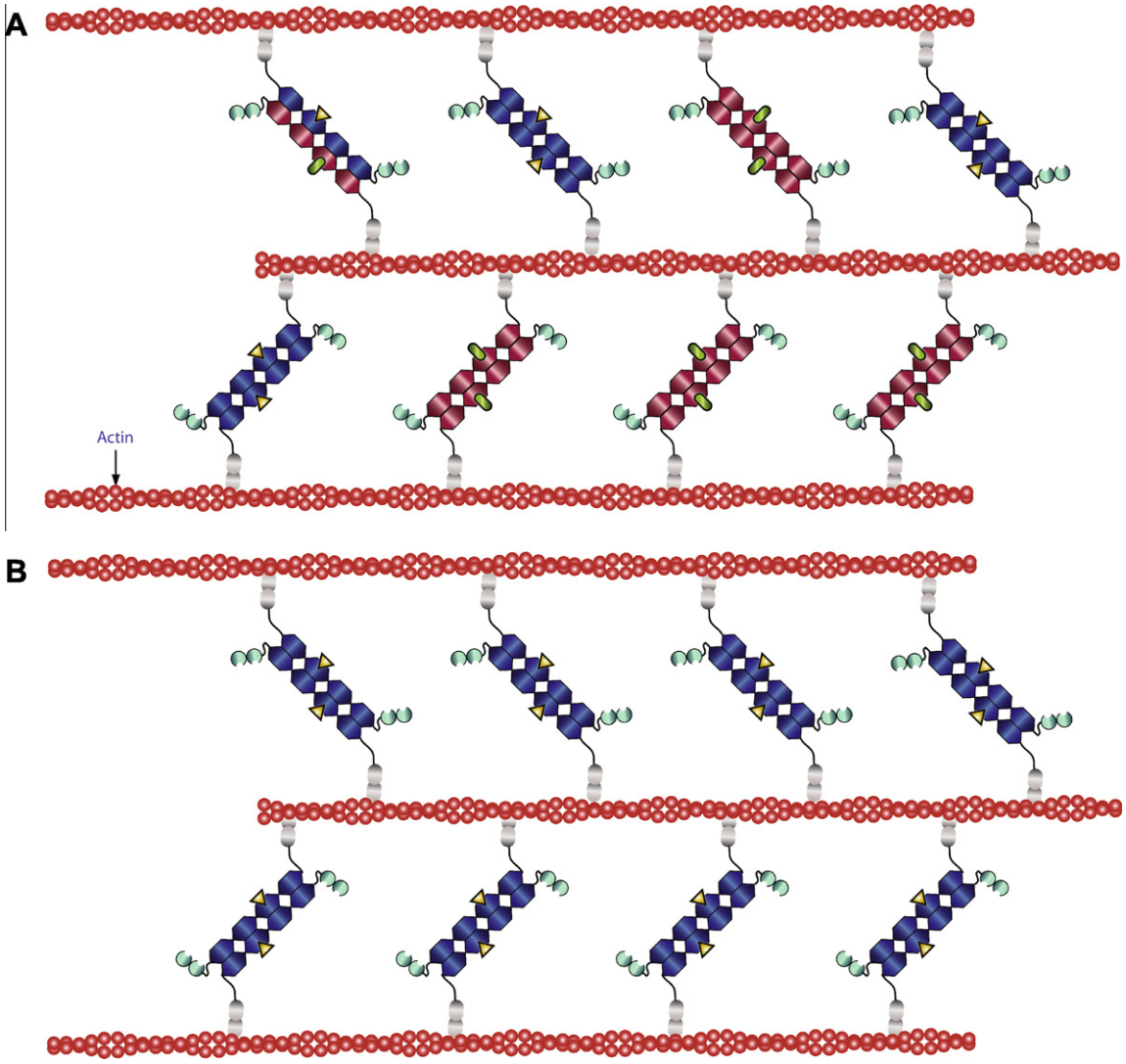

Fig. 2. The sarcomeric actinins dimerise to cross-link actin at the Z-line. The blue and red dimers represent α-actinin-2 and α-actinin-3, respectively. (A) There may be interactions with α-actinin-2 or -3 which are isoform specific. These interactions are represented by a yellow triangle or green rounded rectangle. Within a protein interaction framework, we propose three broad scenarios which can occur in the absence of α-actinin-3. (B) Interactions which are α-actinin-3 specific are lost. (C) Interactions which are α-actinin-3 specific still occur but with reduced binding affinity. This may effect the activation threshold of sensors at the membrane. (D) Fast fibres that are deficient in α-actinin-3 are more susceptible to damage and may release sensors that normally localize to the Z-line.

and $Na_v1.5$ [34], which function to increase the overall channel currents. (2) α-Actinin is required for channel activation of polycystin-2 [35], TRPP3 [36] and the L-type Ca^{2+} channels [37]. (3) α-Actinin plays an essential role in the insulin and phosphorylation dependent transport of GLUT4 [38] and AMPA receptor subunit Glu4 [39], respectively. (4) α-Actinin has the ability to interact with multiple proteins simultaneously and is thought to act as a molecular bridge between SK2 and L-type Ca^{2+} channels and also between β-integrin and dystrophin. In the case of SK2 and L-type Ca^{2+} channel this allows the calcium activated SK2 channel to be in close proximity to a source of Ca^{2+} ions [40]. In contrast, the bridge between β-integrin and dystrophin provides a link between the muscle cytoskeleton and the extra-cellular matrix allowing mechanical force to be transduced along this link [41]. (5) α-Actinin can act to modulate the behaviour of a receptor through competitive binding. For example, α-actinin and calmodulin compete for the same interaction sites on the NMDA NR1 subunit. At resting intracellular calcium levels, α-actinin binds to NR1 and is displaced and inactivated by calmodulin at higher calcium levels [42].

All of the above interactions were characterized using α-actinin-2 except for AMPA and GLUT4 which were shown to interact with the non-muscle actinins, α-actinin-1 and -4 respectively. Although the four α-actinins are highly similar, subtle sequence differences may be mediating isoform specific interactions. There are three reports of functional differences between the different α-actinin isoforms: (1) GLUT4 transport was reported to be α-actinin-4 dependent, while down-regulation of α-actinin-1 had no effect on transport [38]. (2) Expression of chicken α-actinin-2 and not non-muscle α-actinin was able to reduce the inactivation of the L-type Ca^{2+} channel [37]. (3) Adenosine A_{2A} receptor shows a binding preference to α-actinin-3, however there are no reports on functional significance of this preference [31]. Therefore, given the ability of α-actinins to modulate sensor behaviour at the membrane, it is possible that substitution and up-regulation with another α-actinin isoform may also have the ability to alter sensor behaviour at the muscle Z-line.

3. Mechanical sensor

The Z-line proteins, titin, telethonin/TCAP and muscle LIM protein (MLP) have been proposed to play a role in mechanical sensing in the heart [21]. Within the heart this sensor detects

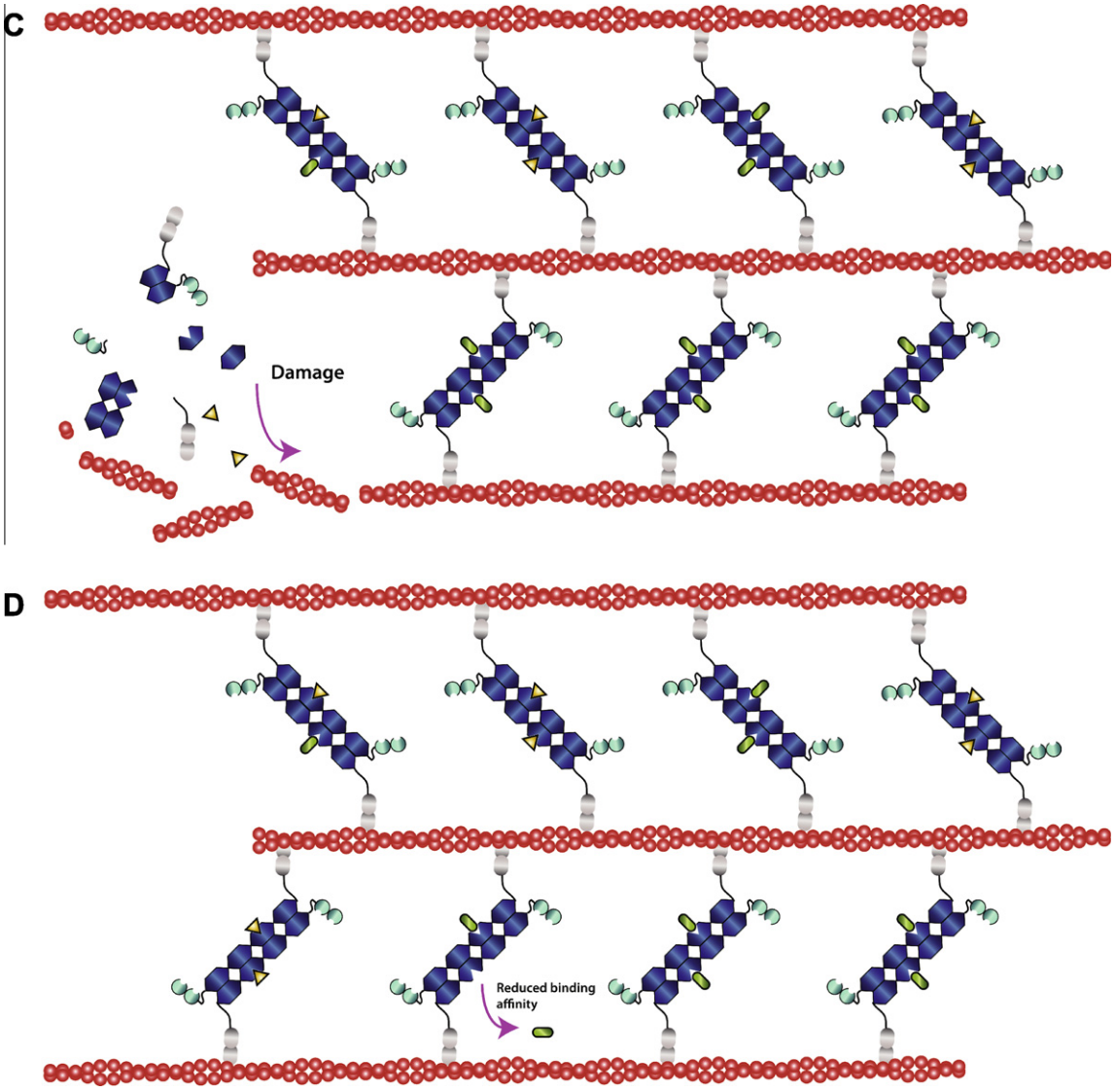

Fig. 2 (*continued*)

biomechanical stress and responds by activating pathways that enhance myocardial cell survival which prevents dilated cardiomyopathies [43]. Despite α-actinin-2 interacting with both titin and MLP and *ACTN2* mutations resulting in cardiomyopathy, the role of α-actinin-2 in the stretch sensor has been largely neglected.

MLP, (also known as cysteine rich protein CRP3), is predominantly expressed in striated muscle and localizes to the cytoplasm [44], nucleus [45] and myofibrillar structures [46]. The interaction between MLP and α-actinin allows MLP to be localized at the Z-line [28] from which it can detect and respond to mechanical stimuli [47]. A recent study proposed that MLP predominately localizes to the cytoplasm and not myofibrillar structures. This suggests MLP may not be localized in a position to receive mechanical signals and instead acts as a signal transducer for the mechanical sensor [44]. MLP has the ability to translocate to the nucleus and activate myogenic transcription factors which include MyoD, myogenin and MRF4 [48]. Thus, MLP mediates the activation of myogenic gene programs upon receiving or transducing mechanical stimuli. There are a number of lines of evidence to suggest that absence of α-actinin-3 or up-regulation of α-actinin-2 may alter the function of the mechanical sensor, MLP and lead to reduced type 2B muscle fibre size and reduced muscle mass in α-actinin-3 deficient muscle. First, the site of α-actinin interaction on MLP is close to a predicted nuclear localize signal (NLS) which may tether MLP to the Z-line and only unmask the NLS when transport to the nucleus is required. Second, interaction with MLP is lost in the α-actinin-2 Q9R mutation resulting in dilated cardiomyopathy [28]. In addition, recently identified mutations in α-actinin-2 may also effect the binding to various proteins within the mechanical sensor machinery [49]. Conversely, cardiomyopathy-causing mutations in MLP [29] and titin [30] result in reduced binding affinity for α-actinin-2. Finally, the over expression of myogenin (an activation target of MLP) activates expression of genes involved in oxidative metabolism and a decrease in type 2B fibre size [50].

4. Calcium sensor

The calcium ion is an essential intra-cellular signalling molecule which varies in concentration during contraction in muscle [51]. This allows muscle to use intra-cellular calcium concentrations as a measure of muscle activity and adapt accordingly. Within muscle the calcium/calmodulin-dependent phosphatase, calcineurin is the major calcium sensor responsible for fibre type switching and hypertrophy [52]. At the muscle Z-line, calsarcins and atrogin-

1 form two important complexes involved in modulating the calcineurin pathway. The α-actinins interact with calsarcin and atrogin-1 and thus modulation of the calcineurin pathway in the *Actn3* KO may contribute to the shift to a more oxidative muscle phenotype and reduced type 2B fibre size.

The calsarcins (also known as FATZ and myozenin) contain three family members, calsarcin-1 which is expressed in heart and type 1 muscle fibres and calsarcin-2 and -3 which are predominantly expressed in type 2 muscle fibres [53–55]. The main function of calsarcins is to inhibit and localize calcineurin to the Z-line through interaction with α-actinin [56]. Hence, the ablation of the calsarcins results in the activation of the calcineurin pathway which is observed in the calsarcin-1 [57] and -2 KO mice [58]. As a consequence, there is a fibre type switch towards slow oxidative fibres thought to underlie the enhanced endurance capacity in the calsarcin-2 KO mouse. In fact, the *Actn3* and calsarcin-2 KO are the only two examples to date where loss of function has resulted in an enhanced endurance phenotype [58]. The calsarcins contain multiple overlapping interaction sites facilitating the interaction with α-actinin, filamin C, telethonin, calcineurin [53] and the PDZ/LIM family [59]. The overlapping binding sites on the calsarcins creates competition between binding partners which is observed with α-actinin inhibiting the binding of filamin C in a dose-dependent manner [55]. Interestingly, α-actinin and calcineurin also have an overlapping binding site [53] and thus competition for this site may be affected by the absence of α-actinin-3 or up-regulation of α-actinin-2.

The muscle and cardiac specific F-box protein, atrogin-1/muscle atrophy F-box (MAFbx) forms the targeting component of the SCF ubiquitin ligase complex [60]. Overexpression of atrogin-1 targets MyoD for degradation resulting in myotube atrophy. Conversely, atrogin-1 deficient mice are resistant to muscle atrophy [61]. In skeletal muscle, atrogin-1 localizes to the Z-line through its interaction with α-actinin. Atrogin-1 modulates the calcineurin pathway by interaction and ubiquitination of calcineurin A, hence targeting it for degradation [62]. Interestingly, the α-actinin interaction site on atrogin-1 is in close proximity to the NLS and calcineurin A binding site [62], suggesting a possible role for α-actinin in regulating the translocation of atrogin-1 to the nucleus where it can target MyoD [63] and myogenin [64] for degradation.

5. Metabolic sensor

In skeletal muscle the metabolic processes of glycolysis and glyconeogenesis are thought to be compartmentalised within the I-band and Z-line, respectively [65]. The glycolytic enzymes, phosphofructokinase, aldolase and pyruvate kinase achieve this through their binding affinity for thin filament proteins such as actin [66], while the glyconeogenesis complex is formed at the Z-line through attaching to sarcomeric α-actinin [67]. The metabolic enzymes, glycogen phosphorylase [68], glycogen synthase [69] and fructose 1,6-bisphosphatase (FBPase) [67] localize to the Z-line, however only the key enzyme of glyconeogenesis, FBPase acts as a metabolic sensor.

The glyconeogenesis complex is composed of FBPase, aldolase and α-actinin [67]. Within the complex, FBPase acts as a metabolic sensor, which senses and is inhibited by the metabolites, fructose 2,6-bisphosphate and AMP. The formation of the complex is regulated by calcium levels and cannot form when calcium concentration is high [70]. Thus, FBPase-mediated glyconeogenesis only occurs during times of recovery or inactivity. In addition to calcium regulation, AMP and fructose 2,6-bisphosphate inhibition prevents the unnecessary consumption of ATP (futile cycle). The interaction between FBPase and aldolase serves two purposes. First, muscle FBPase is strongly inhibited by AMP and should have no activity in muscle, however the interaction with aldolase removes this inhibition [71]. In addition, the interaction with aldolase attached to fructose 1,6-bisphosphate allows FBPase to be in close proximity to its substrate (channelling) [72]. The interaction between FBPase and the sarcomeric α-actinins allows the glyconeogenic complex to be localized at the Z-line in skeletal [67] and cardiac muscle [73]. Besides localize to the Z-line, muscle FBPase also localizes to the nucleus in a developmental dependent manner [74], however its exact function in the nucleus is unknown.

In the *Actn3* KO mouse, there is upregulation of α-actinin-2 to compensate for loss of α-actinin-3 which appears to alter the interaction with the metabolic sensor, FBPase. This may explain the increase in glycogen content and activity in enzymes involved in aerobic metabolism associated with α-actinin-3 deficiency. There are several lines of evidence to support this. In smooth muscle, cytoplasmic FBPase does not localize to non-muscle actinins [75] suggesting the interaction between muscle FBPase is specific to sarcomeric actinins. Furthermore, FBPase complex formation is insensitive to calcium at the cardiac intercalated disc [73], which suggests α-actinin-2 (the only sarcomeric actinin in the heart) has altered interaction properties. In addition, although the interaction sites on α-actinin and FBPase have not been determined, α-actinin may play an additional role in masking the NLS of FBPase [76] preventing its translocation to the nucleus while attached at the Z-line. While the role of FBPase in the nucleus is unknown, cellular localization of liver FBPase has been linked to glycogen formation [77]. Last, FBPase activity in mouse muscle was only detected in fast muscle fibres, with glycolytic fibres having higher activity [78]. Hence, expression of FBPase is fast fibre specific or requires fast fibre specific proteins in order to be active. We have proposed that α-actinin-3 has functionally diverged from α-actinin-2 after gene duplication resulting in fast fibre specific interactions and functions [26]. Similarly, there may be additional functional divergence from liver FBPase besides AMP inhibition [79] which has given muscle FBPase tissue specific functions. The alteration in muscle metabolism observed in the muscle phosphofructokinase (PFK) KO mice (PFK is activated by fructose 1,6-bisphosphate) [14] and PEPCK-C (another key enzyme in glyconeogenesis) transgenic mice [80] provides a precendent for possible alterations caused by muscle FBPase.

6. Conclusion

The actinins play a role in modulating the function of sensors at the membrane and in this review we have highlighted evidence which suggests actinin may also modulate sensor behaviour at the Z-line. The alterations of mechanical, calcium and metabolic sensors at the Z-line results in possible phenotypes which are common to those observed in α-actinin-3 deficiency. Within a protein interaction framework, absence of α-actinin-3 could result in loss of interactions or new interactions with α-actinin-2 which normally do not occur in fast muscle fibres [26]. In addition, up-regulation of α-actinin-2 expression may also affect stoichiometry in which protein complexes form. The ability of α-actinin to dock proteins to the Z-line preventing their transport to the nucleus is common to all sensing machinery above. In addition, sarcomeric actinins play a similar docking role in their interaction with the myopodin signalling complex [81], FHL3 [82] and the downstream targets of MEF2A, myomaxin [83] and myospryn [84]. In the *Actn3* KO, there is up-regulation of desmin, myotilin and αβ-crystallin [unpublished data], which likely reflects myofibrillar remodelling [85]. In addition, upon eccentric contraction there is an increased suspectibility to damage in α-actinin-3 deficient fibres [unpublished data]. Taken together, structural stability and release of important nuclear shuttling proteins at the Z-line provides an

alternate structural based framework (Fig. 2D). Interestingly, there are other important examples of genetic compensation resulting in altered muscle function. The dystrophin-deficient mdx mouse muscle disease phenotype is more severe when its genetic backup, utrophin is also absent in double KO mice [86]. Similarly, the myotilin-deficient mouse only shows a disease phenotype when its genetic backup, myopalladin is knocked out. Lastly, morbidity in skeletal muscle α-actin deficient mice can be rescued by heterologous expression of cardiac (fetal) α-actin [87]. Therefore, understanding the protein interaction framework surrounding the structural protein, α-actinin will provide insight into the mechanism of genetic backup and its effects on normal muscle variation.

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